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Diaphragm thickness and ICU admission risk in elderly COVID-19 patients: a CT-based analysis

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Abstract

Background The objective of this study was to examine the impact of diaphragm thickness (DT) on the prognosis of elderly patients infected with COVID-19, particularly with regard to the necessity of intensive care unit (ICU) admission.

Methods Between August 2020 and January 2021, 188 patients aged ≥ 65 years who were admitted to the internal medicine department of our hospital with a diagnosis of COVID-19 infection, were included in this study. The patients' DTs of the patients were measured by a radiologist using computed tomography (CT) scans from the right and left diaphragm dome level. DT was compared with the progression of respiratory distress and the necessity of intensive care. In statistical analysis, $p < 0.05$ was considered significant.

Results Right DT was higher in the group of patients with admission to the ICU ($p = 0.11$). According to multivariate logistic regression analysis, ferritin level (OR = 1; 95% CI = 1–1; $p = 0.014$), IL-6 level (OR = 1.004; 95% CI = 1-1.007; $p = 0.045$) and higher right DT (OR = 11.015; 95% CI = 3.739–32.447; $p = 0.035$) were found to be independent risk factors predicting the ICU admission in COVID-19 patients. There was no significant association with left DT. The predictive value of right DT for ICU requirement in COVID-19 patients was evaluated by ROC analysis. The ROC analysis showed a cut-off value > 1.8, AUC = 0.632, $p = 0.009$, 95% CI (0.558–0.701). In correlation analysis, a positive correlation was found between right DT and ICU admission ($r = 0.331$, $p < 0.001$).

Conclusion Our study is the first to evaluate dome-level DT with CT in elderly patients with COVID-19. In the elderly population, higher right DT levels have been observed to enhance the probability of ICU admission. This may be due to the fact that our sample group consists only of elderly people and the effects of COVID-19. We believe that further validation with more comprehensive studies is needed for DT assessment for clinical treatment decisions, particularly in COVID-19 patients. In addition, we think that the proposal for a standardized measurement site and method for DT measurement will be a guide for future studies.

Clinical trial Not applicable.

Keywords Computed tomography, Diaphragm, Thickness, Elderly, COVID-19 infection, Critical care

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Introduction

The novel coronavirus, officially designated as SARS-CoV-2 (COVID-19), has had a profound global impact, leading to a pandemic that has resulted in significant mortality and morbidity. The group most affected by COVID-19 and with the highest mortality rate are elderly patients [1, 2, 3]. Elderly patients are more vulnerable to all kinds of external stress and interference than younger patients. ICU hospitalizations in the elderly bring additional risk factors that increase mortality and morbidity, especially delirium. Protection of the elderly patient from this condition is more significant than effective care in the ICU [4, 5, 6, 7, 8]. In COVID-19 infection, respiratory distress has been the most challenging situation for clinicians. In these patients, respiratory distress, respiratory muscle dysfunction and the intubation process are the major contributors to mortality [9, 10].

The diaphragm is the primary respiratory muscle and plays a pivotal role in maintaining respiratory homeostasis. Like other muscles in the human body, it is susceptible to the effects of ageing and sarcopenia [11]. Sarcopenia and diaphragm weakness are conditions that become more prevalent with age. Impaired diaphragm performance is associated with an unfavourable prognosis for patients, regardless of the degree of diaphragm dysfunction. For example, conditions such as hypoxic stress, critical illness, cancer cachexia, chronic obstructive pulmonary disease (COPD) and age-related sarcopenia, are characterised by significant diaphragm muscle dysfunction [12]. Diaphragm thickness (DT) has been evaluated in ICU patients in many studies and used as a parameter for weaning the patient from mechanical ventilation [13, 14]. There are also DT-related studies evaluating intubation and mortality in patients with COVID-19 [15, 16, 17]. The majority of extant studies posit that the thinning of the diaphragm muscle exerts an adverse effect on respiration and the patient's prognosis. However, there are studies demonstrating that there is no difference in mortality and prognosis between groups with and without a decrease in DT. Furthermore, there are a limited number of studies showing that an increase in DT is associated with unfavorable outcomes. These results may be due to the difference in measurement methods [13, 18]. DT measurement can be performed by many different methods such as ultrasonography (USG), CT and magnetic resonance imaging (MRI). The use of CT for DT measurement in COVID-19 patients appears to be safer and more convenient than other methods. Thorax CT has been a frequently used method to demonstrate lung involvement, determine its severity, guide treatment and evaluate response to treatment, especially during the COVID-19 pandemic [19]. However, there is no standard recommendation for the location and method of DT measurement with CT. A limited number of studies have measured the thickness of the hemidiaphragm in coronal sections at the level of the celiac trunk, from both the mid and posterior vertebral body levels [15, 16, 20]. Furthermore, there are studies where the DT was measured at the level of the right and left hemidiaphragm dome [21, 22].

In this study, we aimed to investigate the relationship between diaphragm thickness, the most important muscle of respiration and prognosis in elderly patients with COVID-19 infection, an important disease involving the respiratory system. We also hoped to contribute to the literature in terms of standardization of tomographic measurement of DT.

Materials and methods

This is a retrospective cross-sectional study. Our study was approved by Ministry of Health, Provincial Health Directorate, Ankara Bilkent City Hospital, Ethics Committee No. 1. (Date: 25.11.2020, Decision: E1-20-1330). The research was conducted in accordance with the ethical standards set forth in the Declaration of Helsinki

Data collection

The study included 188 patients aged ≥65 years who received inpatient treatment with a diagnosis of COVID-19 between August 2020 and January 2021 in the internal medicine clinics of Ankara Bilkent City Hospital affiliated to the Ministry of Health. The patients' records were analysed retrospectively. Demographic characteristics, laboratory data (haemogram, CRP, procalcitonin, interleukin-6 and ferritin), length of hospital stay, admission for intensive care and excitus status of the patients were recorded.

The data were collected by reviewing patient records and the hospital information system. Patients with a documented history of lung disease, an absence of data, and no chest tomography were excluded from the study. Patients under the age of 65 were excluded to mitigate the potential for confounding variables, including immune response, the impact of physiological changes associated with aging, and comorbidities. These patients were also not utilized as a control group for comparative analysis. Patients with neuromuscular diseases, such as phrenic nerve injury, Guillain-Barré syndrome, myasthenia gravis and myasthenia gravis, which may affect diaphragm function and patients who were mechanically ventilated on admission, were also excluded from the study. DT was measured twice at three-month intervals by a radiologist and averaged (Intraclass correlation coefficient = 0.945, 95%CI 0.897–0.971, $p < 0.001$).

Radiological measurement

All thorax CT studies were conducted using a 128-detector system (GE Revolution, General Electric, Milwaukee, WI), with images captured from the first rib to the adrenal glands, in a non-enhanced state. The following technical parameters were employed: 100 kV, 110 mAs, body filter, 1.25 mm slice thickness, 512 × 512 reconstruction matrix, spiral pitch factor 1.375:1. All CT scans were imported from the Picture Archiving and Communication System of the radiology system and stored on a secure computer system for subsequent analysis.

The image was analysed by a radiologist with 11 years of experience. The analysis was conducted on workstations utilizing bespoke software packages (AW4.7 Ext.13 software, GE, USA). The radiologist measured the dome of the right and left diaphragm thickness in the coronary position, which was reconstructed using a 1 mm thickness image between the ninth and tenth intercostal spaces. Each diaphragm was measured on three occasions by the same radiologist and the mean value of the three measurements was subsequently provided (Fig. 1).

Statistical analysis

The data was analysed using the SPSS 22 software (IBM SPSS Statistics, IBM Corporation, Chicago, IL). The normal distribution of variables was assessed using Shapiro-Wilk tests. Normally distributed variables are presented as mean ± standard deviation, while non-normally distributed variables are presented as median (minimum-maximum) values. When comparing non-categorical parameters between groups, Student's T-test was used for normally distributed parameters and the Mann-Whitney U-test for non-normally distributed parameters. Chi-square or Fisher's exact tests were used for categorical variables. Independent risk factors for the need for intensive care in COVID-19 patients were assessed using the Backward LR method with multivariate analysis, including parameters that created a significant difference between the groups.

Lymphocyte, CRP, procalcitonin, interleukin-6 and ferritin levels, which are laboratory parameters with proven prognostic importance especially in cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, were used in multivariate logistic regression analysis [17, 23, 24, 25]. Multicollinearity was assessed prior to analysis. The multivariate analyses did not include oxygen requirement and hospitalization duration because these variables correlated with laboratory parameters. The right DT in predicting the need for intensive care in COVID-19 patients was analysed using the ROC curve with a 95% confidence interval. Cut-off values predicting

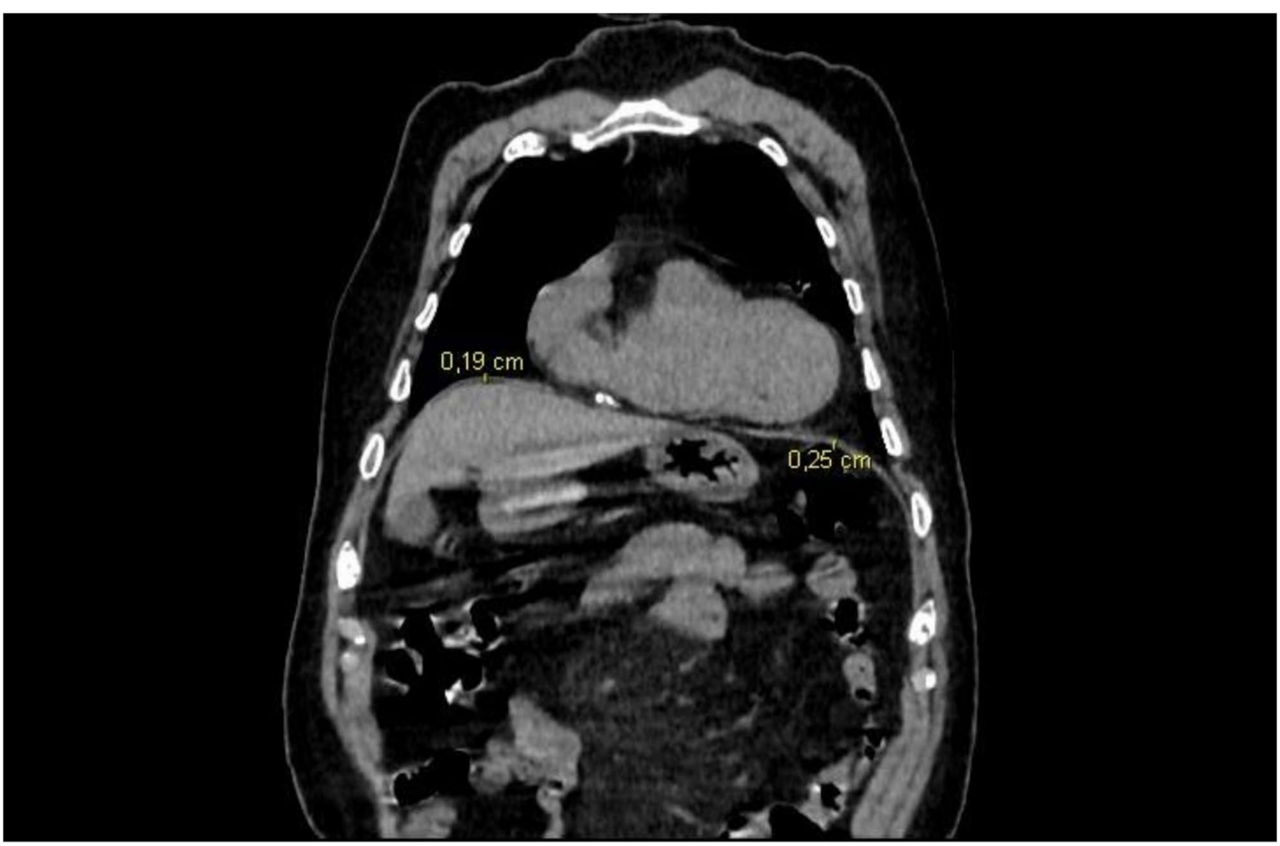

Fig. 1 Right and left diaphragm thickness measurement in the coronary position reconstructed with a 1 mm thick image between the ninth and tenth intercostal space at the level of the diaphragm dome

Table 1 Demographic, clinical, laboratory and radiological characteristics of patients with and without intensive care unit requirement due to COVID-19 disease

	Total ($n = 188$)	Patients without ICU admission ($n = 149$, 79.3%)	Patients with ICU admission ($n = 39$, % 20.7)	p
Demographic data				
Age (median) (min-max)	76(65–96)	75(65–96)	78(65–95)	0.180
Female gender, n (%)	95 (50.5)	75 (50.3)	20 (51.3)	0.916^{x}
Clinical data				
Duration of hospitalisation (days) (Median)(min-max)	12 (3–40)	10 (3–36)	16 (6–40)	**$<0.001^{m}$**
Presence of oxygen requirement, n (%)	122 (64.9)	88 (59.1)	34 (87.2)	**0.001^{x}**
Exitus, n (%)	33 (17.6)	12 (8.1)	21 (53.8)	**$<0.001^{x}$**
Additional diseases				
Hypertension, n (%)	142 (75.5)	112 (75.2)	30 (76.9)	0.820^{x}
Diabetes Mellitus, n (%)	76 (40.4)	60 (40.3)	16 (41)	0.932^{x}
COPD:, n (%)	55 (29.3)	42 (28.2)	13 (33.3)	0.529^{x}
CAD, n (%)	85 (45.2)	65 (43.6)	20 (51.3)	0.392^{x}
Dementia, n (%)	19 (10.1)	15 (10.1)	4 (10.3)	0.972^{x}
Hypothyroidism, n (%)	15 (8)	12 (8.1)	3 (7.7)	0.941^{f}
Chronic renal failure, n (%)	18 (9.6)	12 (8.1)	6 (15.4)	0.166^{f}
Laboratory data				
Lymphocyte (10^9/L) (Median)(min-max)	920 (160–8210)	960 (160–8210)	800 (330–2770)	**0.500^{m*}**
CRP (gr/L) (median)(min-max)	78 (1-291)	82.6 (1-269)	56.6 (5.5–291)	0.219^{m}
Procalcitonin (µg/L) (median)(min-max)	0.1 (0–20)	0.1 (0–20)	0.2 (0.03–2.5)	**0.019^{m}**
Maximum ferritin level (µg/L) (Median)(min-max)	571 (24-29467)	543 (24-12391)	989 (47-29467)	**0.006^{m}**
Lactate (mmol/L) (Median)(min-max)	1.6 (0.02–4.9)	1.6 (0.02–4.9)	1.5 (0.5–3.7)	0.197^{m}
Maximum interleukin-6 level (pg/mL) (median)(min-max)	571 (24-29467)	26.3 (0.1–759)	33.3 (3.6–1000)	**0.048^{m}**
Radiological findings				
Right DT (mm) (Mean ± SD)	1.8 ± 0.4	1.7 ± 0.4	2 ± 0.4	**0.011^{t}**
Left DT (mm) (Mean ± SD)	1.8 ± 0.4	1.8 ± 0.4	1.8 ± 0.4	0.342^{t}

COVID-19: coronavirüs Disease 19 COPD: Chronic Obstructive Pulmonary Disease, CAD: Coronary Artery Disease, CRP: C reactive protein, DT: diaphragm thickness, ^{m}: Mann Whitney U Testi, ^{t}: Student't T Testi ^{x}: Ki-kare Testi, ^{f}: Fisher's Exact Testi

the need for ICU were calculated with the Youden Index. p values below 0.05 were considered statistically significant.

Results

Of the 188 COVID-19 patients included in the study, 95 (50.5%) were female. The mean age was 76 (65–96) years; 149 (79.3%) patients were in the group without ICU admission, while 39 (20.7%) patients were in the group with ICU admission. Duration of hospitalisation ($p < 0.001$), oxygen requirement ($p = 0.001$), presence of excites ($p < 0.001$), lymphocyte level ($p = 0.500$), procalcitonin level ($p = 0.019$), maximum ferritin level ($p = 0.006$), maximum IL-6 level ($p = 0.048$), and right DT ($p = 0.011$), were higher in the group of patients requiring ICU. No difference in left DT was found between the groups ($p = 0.342$). Demographic, clinical, comorbidity, laboratory, treatment and radiological data of the patients are shown in Table 1.

In our study, according to multivariate logistic regression analysis, ferritin level (OR = 1; 95% Cl = 1–1; $p = 0.014$), IL-6 level (OR = 1.004; 95% Cl = 1-1.007; $p = 0.045$) and right DT elevation (OR = 11.015; 95% Cl = 3.739–32.447; $p = 0.035$) were found to be independent risk factors predicting the need for intensive care in COVID-19 patients (Table 2).

Table 2 Determination of risk factors related to ICU admission in patients with COVID-19 by multivariate logistic regression analysis

	OR (% 95 GA)	p
Lymphocyte (10^9/L)	1 (0.999-1)	0.761
Maximum ferritin level (µg/L)	1 (1–1)	**0.014**
Maximum interleukin-6 level (pg/mL)	1.004 (1-1.007)	**0.045**
Procalcitonin (µg/L)	1.004 (0.702–1.216)	0.573
Right DT (mm)	11.015 (3.739–32.447)	**0.035**

DT: diaphragm thickness

The predictive value of right DT for the need for intensive care in COVID-19 patients was evaluated using ROC analysis. The ROC analysis showed a cut-off value > 1.8, AUC = 0.632, $p = 0.009$, 95% Cl (0.558–0.701). Right DT > 1.8 mm had 64.1% sensitivity and 59.1% specificity for intensive care admission (Fig. 2). However, the diagnostic performance of the left DT was not sufficient for admission to the intensive care unit. ROC analyses

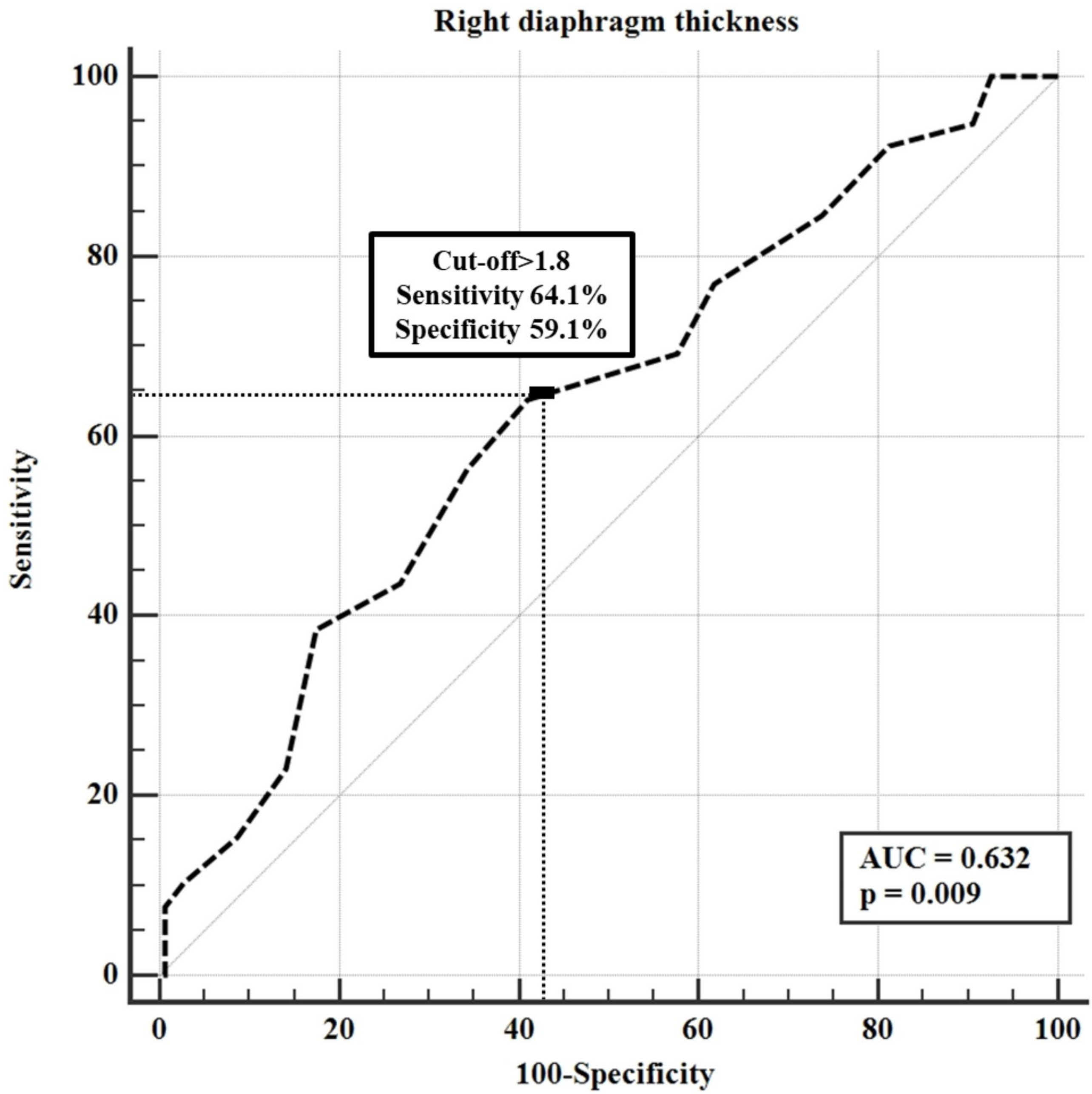

Fig. 2 Receiver operating characteristic (ROC) curve of right diaphragm thickness (DT) for predicting ICU admission rate. Receiver operating characteristic analysis to assess the predictive power of right DT revealed a cut-off value of 1.8 mm (AUC = 0.632, 95% CI [0.558–0.701] $p = 0.009$) for ICU admission rate. AUC: area under the curve, CI: confidence interval

showed no significant change in diagnostic performance when right DT was combined with procalcitonin, ferritin or IL-6 parameters (Table 3). Correlation analysis showed a positive correlation between right DT and need for intensive care ($r = 0.331$, $p < 0.001$).

Discussion

The diaphragm is the most important muscle for respiration and changes can occur in the diaphragm, as in any organ, with aging. The elderly population is predisposed to respiratory diseases and exhibits elevated mortality and hospitalization rates [4]. In this study, we examined the prognostic significance of DT in elderly patients with COVID-19, an important respiratory infection. A review of the extant literature revealed no studies that

Table 3 ROC analyses for intensive care unit admission

Parameters	AUC	95%CI	Cut-off	*p* value	Sensitivity	Specificity
Right DT	0.632	0.558–0.701	> 1.8	**0.009**	64.1%	59.1%
Left DT	0.507	0.433–0.581	> 1.7	0.887	66.7%	43.0%
PCT	0.610	0.535–0.680	> 0.15	**0.038**	53.8%	66.4%
Max ferritin	0.542	0.468–0.614	≤ 510	0.412	76.9%	38.3%
Max IL-6	0.596	0.502–0.684	> 119	0.108	22.9%	98.8%
Right DT + PCT	0.621	0.547–0.691	-	**0.019**	64.1%	59.6%
Right DT + max ferritin	0.650	0.577–0.718	-	**0.002**	51.3%	75.8%
Right DT + max IL-6	0.614	0.521–0.702	-	0.062	34.3%	94.1%

DT: diaphragm thickness IL-6: interleukin-6, PCT: Procalcitonin

had evaluated DT with tomographic examination exclusively in elderly patients and in this respect, this study is the first [26]. The cut-off for right DT was 1.8 mm and we found a positive correlation between right DT and ICU admission.

There was no significant association between left DT and ICU admission. We thought that this might be due to the structure of the left DT, the presence of the heart in that region and the different degree of contribution to respiration.

In our study, the finding that high right DT levels predicted the need for ICU shows some differences with the existing literature. This phenomenon was hypothesized to be attributable to numerous factors. These included the different method and location of DT measurement, the effects of COVID-19 infection, and the fact that the sample group consisted only of elderly people.

In a study by Parlak et al. of 404 COVID-19 patients, DT was measured at the level of the celiac artery trunk and decreased DT was found to be associated with poor prognosis. In this study, the mean age was 49.2 years and there was a weak correlation between DT and age [15]. In a similar study by Dal et al., low DT in ICU patients was found to be lower in patients who required intubation and died [17].

Hadda et al. performed daily DT measurements with USG in non-intubated COVID-19 patients within five days of hospitalization and found a temporal decrease in DT. In this study, the authors measured DT at the right and left dome level. The sample consisted of 64 patients with a mean age of 50.2 years [27]. In the present study, chest CT scans of patients were evaluated during their initial hospitalization. Consequently, the current findings belong to the initial period of the disease. The current DT increase can be attributed to the active phase of the disease. Possible causes such as hypertrophy mechanisms via ACE receptors, defined as the COVID-19 receptor, and cytokine storm may account for this result. It is not known whether the current increase continues. Due to the absence of control CT results in our study, it is not possible to provide definitive statements regarding this issue. DT is influenced by numerous factors. Farr et al. evaluated the maximum expiratory and end-inspiratory thicknesses of the diaphragm muscle with USG during patient follow-up after COVID-19 and showed a significant decrease in muscle contraction. This study highlights the prolonged effects of COVID-19 and its contractile function as well as thickness [28]. In another USG-based study, Umbrello et al. evaluated the diaphragm muscle and the rectus femoris muscle together and found that the decrease in muscle mass and changes in muscle structure were associated with protein deficiency and fluid balance [29]. In these studies, the sample size was selected from the general population and no special evaluation was made exclusively for the elderly. Consequently, the findings of the present studies appear to be inadequate for the purpose of generalization to elderly patients. In addition, DT measurement methods and locations are different, so it is not possible to make a reliable comparison.

In studies comparing respiratory muscle strength and DT with sarcopenia in the elderly, it has been shown that DT is reduced in sarcopenic elderly. However, the sample sizes in these studies are quite small, with 45 and 60 subjects, respectively [30, 31]. Among the studies with COVID-19 in the literature, there were limited studies evaluating sarcopenia with DT. These studies used USG to assess both the diaphragm and peripheral muscles [29, 32, 33].

The mechanisms responsible for age-related diaphragm sarcopenia are not yet fully understood, however the extant literature has yielded divergent results and the neuromuscular mechanism is the most emphasized of these. A number of studies have investigated neuromuscular transmission using a general measure of the force generated by the diaphragm muscle in response to nerve and direct muscle activation, during aging. The results of the study indicate that alterations in neuromuscular transmission occur prior to the onset of diaphragm muscle weakness or substantial muscle fiber atrophy [34]. A recent study in mice with a model of premature aging found a state of diaphragm hypertrophy that contradicts previous literature. Indeed, in the early stages of the aging process, a phenomenon of muscle remodelling is observed, where the body tries to repair damaged fibers and mimics the effects of hypertrophy (pseudohypertrophy). A similar study was conducted on younger elderly people without a history of falls. In that study, diaphragm muscle thickening was evaluated using ultrasound and it was found that the diaphragm muscle thickened in the elderly [11, 35]. A multitude of factors have been demonstrated to contribute to loss of muscle mass and dysfunction in animal models. These factors include hypercapnia, hypoxia, acidosis, smoking, metabolic disorders, comorbidities, nutritional abnormalities, genetic predisposition, medications, systemic inflammation, aging and inactivity. It is important to consider these factors when addressing muscle loss and dysfunction. Given the accumulated knowledge in this field, it is evident that a multitude of factors influence diaphragm muscle mass and function, particularly in elderly patients [12].

The angiotensin-converting enzyme-2 (ACE2) receptor has been identified in studies as the entry receptor of the virus causing COVID-19. Specifically, on diaphragm muscles, ACE2 functions as a master regulator of the renin angiotensin system (RAS), mainly by converting Ang (angiotensin) I and Ang II to Ang 1–9 and Ang 1–7, respectively. The effects of pathways driven by ACE2/Ang 1–7 include adverse fibrosis, hypertrophy, increased reactive oxygen species (ROS) and vasoconstriction [36]. Overactivation of the Ang 1-7-Mas pathway has been shown to reduce muscle weakness in aged mice [37]. In a postmortem study involving COVID-19 intensive care patients, ACE-2 expression and SARS-CoV-2 viral infiltration in the human diaphragm were examined and the results showed increased expression of genes involved in fibrosis in the diaphragm and histological evidence of fibrosis development [38]. In another study examining the relationship between COVID-19 and diaphragm myopathy, the diaphragms of critically ill patients showed extremely large myofibers that histopathologically divided and contained many central nuclei [39]. The sample sizes in these postmortem studies were minimal and no measurements of DT were recorded. Therefore, these results can be accepted as a hypothesis. Nevertheless, these results suggest that COVID-19 through the ACE2 receptor has effects on the diaphragm muscle different from other infections. This finding may offer a partial explanation for the observed increase in DT among patients requiring intensive care. However, it is important to note that this explanation is not definitive. Nevertheless, given the prevalence of hypertension and the use of ACE inhibitors in elderly patients, as well as the associated upregulation of ACE receptors, the potential effects of ACE receptors should not be disregarded [40].

Although studies have generally found that decreased DT is associated with ICU admission and mortality, there are different results. Branea et al. in their study in which patients with COVID-19 were evaluated in two groups as patients with and without a decrease in DT, no significant difference was found between the groups in terms of intensive care unit admission and mortality [41]. In the study by Goligher et al., there was both a decrease and an increase in diaphragm thickness in patients followed up with mechanical ventilation. These two conditions were found to be associated with negative outcomes. In this study, DT was measured and evaluated from the dome level, just as in our own study [13].

Evaluation of right DT in combination with other prognostic factors will provide more information in terms of predicting the need for ICU. In our study, to increase the specificity of right DT in predicting ICU admission, DT was evaluated together with lymphocyte, ferritin, interleukin-6, and procalcitonin levels, which have been reported to be prognostic for COVID-19. A significant increase in specificity was also found with ferritin. In very large-scale meta-analyses examining the prognostic relationship between COVID-19 and laboratory parameters, ferritin has been emphasized as an important prognostic marker. Ferritin cut off value is generally accepted to be above 500 μg/L and even set as a treatment target [42, 43]. In addition, a weak positive correlation was found between increased right DT and ICU admission. It was thought that this relationship was related to the elderly sample group and should be evaluated together with other parameters.

Especially in COVID-19 studies, it was observed that tomographic DT measurements were made by measuring the celiac artery trunk at the crus level. However, when the literature was examined, it was seen that there are also studies measured from the dome level, as in our study [13, 21]. Gatti et al. conducted a study in which they measured the thickness of the diaphragm using tomography, at both the dome and crus levels. They then investigated the relationship between these measurements and ultrasonographic measurements [44]. In a meta-analysis comparing ultrasound and non-ultrasound imaging techniques in the evaluation of diaphragmatic dysfunction, DT measurement methods were divided into static and dynamic. Static methods include brightness mode (B-mode) ultrasound, chest radiography, CT and static MRI; dynamic methods include motion mode (M-mode) ultrasound, fluoroscopy and dynamic MRI. It is important to note that the DT measurement site differs in each of these methods. In general, studies have addressed different sample groups, namely intensive care patients, different lung infections and mechanical ventilation conditions [26]. In addition, the diaphragm has a very different muscular structure. Firstly, it is divided into a right and a left hemidiaphragm. The peripheral part of the diaphragm consists of muscle fibres, while the central part (tendon) consists of noncontractile aponeurosis.

Muscle fibres are divided into three parts: the vertebral part, the costal part and the sternal part. The vertebral portion consists of two crus and arcuate ligaments. The costal portion originates from the lower six costae and costal cartilages, while the sternal portion originates from the xiphoid process of the sternum. The peripheral muscle fibres join together in the middle part of the diaphragm to form the central tendon, which can be likened to a three-leaf clover. The right and left leaflet form the dome, while the upper side of the anterior leaflet is partially fused with the pericardium. The diaphragm is surrounded by thin layers of pleura and peritoneum [45, 46, 47]. In light of the distinct structural characteristics of the diaphragm, Haaksma et al. undertook a comprehensive study. Utilizing ultrasonography (USG), they measured the diaphragm's thickness (DT) from multiple regions and sought to delineate the optimal measurement site [48].

Consequently, it may be unwise to generalize and evaluate an organ with such divergent anatomy and physiology by measuring it from a single location. In addition, the effects of COVID-19 on the diaphragm muscle are still not clearly known. Although conditions such as ACE and related fibrosis, known as COVID-19 and its entry receptors into the body, conditions such as excessive immune response results, cytokine storm, etc. have been studied, there are no definitive results [49, 50].

Current research on the correlation between COVID-19 and diaphragm thickness is limited. Diaphragm muscle mass and function are affected by many factors, notably age. In addition, there is no standardisation for the measurement of diaphragm thickness, measurement site and measurement technique. We believe that a reliable standardisation according to age, comorbidities and measurement site is needed in order to evaluate DT measurement in all patients in the same way.

Limitations

Our study had several limitations. First, it was retrospective, the sample size was small and it was single centered. Another limitation was the inability to establish a cause-and-effect relationship due to the cross-sectional study design.

The measurement of DT was executed using a methodology that is comparatively infrequently employed within the extant literature. In the absence of a comparable study that has evaluated DT with this methodology in patients diagnosed with COVID-19, a comprehensive comparison that incorporates our established cut-off values was not feasible. CT scans were performed at the time of initial admission and no follow-up imaging was performed to check for changes.

The use of a single measurement method was also a limitation. Comparison of DT measured from both the dome level and the celiac artery level in future studies using CT may be a design for future studies. In addition, we believe that first evaluating and comparing DT measurement with both dynamic and static methods in healthy groups may guide future studies for standardization of DT measurement method.

Conclusion

This study is among the first to evaluate DT using CT at the dome level in elderly COVID-19 patients. Our findings indicate that elevated right DT levels are associated with an increased risk of intensive care admission in elderly individuals. This observation may be attributable to the composition of the sample group, which exclusively comprised elderly individuals and the repercussions of the COVID-19. In accordance with the findings of our study, an examination of the extant literature suggests a need for more comprehensive studies to assess the efficacy of DT for clinical treatment decisions, particularly in patients with COVID-19. In addition, since the diaphragm is a very heterogeneous organ in terms of muscle groups and tendon structure, we think that more comprehensive studies comparing dynamic and static measurement methods are needed to suggest a standardized measurement site and method for DT measurement. Finally, we would like to draw attention to the fact that elderly patients should be evaluated differently from the normal population in terms of physiological organ dysfunctions that occur with aging.

Abbreviations

COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
DT	Diaphragm muscle thickness
ICU	Intensive care unit
MRI	Magnetic resonance imaging
USG	Ultrasonography

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None.

Author contributions

MT, CO, EO, GA, KS and IA contributed to the conception, design of the work and the acquisition, analysis, interpretation of data, and the drafting and revision of the work, and final approval of the work. All authors had the data access and contributed to the article. All authors agree to publish the article and to be responsible for all aspects of the work.

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Data availability

Data supporting the findings of this study can be obtained but there are restrictions on the availability of these data, these data were used under license for the current study and are therefore not publicly available. However, data can be obtained from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Our study was approved by Ministry of Health, Provincial Health Directorate, Ankara Bilkent City Hospital, Ethics Committee No. 1. (Date: 25.11.2020, Decision: E1-20-1330). The research was conducted in accordance with the ethical standards set forth in the Declaration of Helsinki. This is a retrospective cross-sectional study. Informed consent forms were obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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